(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 May 2005 (19.05.2005)

PCT

(10) International Publication Number
WO 2005/044285 A1

(51) International Patent Classification[7]: A61K 31/74

(21) International Application Number:
PCT/KR2004/002837

(22) International Filing Date:
4 November 2004 (04.11.2004)

(25) Filing Language: Korean

(26) Publication Language: English

(30) Priority Data:
10-2003-0079065
10 November 2003 (10.11.2003) KR

(71) Applicant *(for all designated States except US)*: **BIORANE CO., LTD** [KR/KR]; Hanyang institute of technology 3rd Fl., Hanyang University, 17 Haengdang-dong, Seongdong-gu, Seoul 133-791 (KR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KIM, Jin-Hong** [KR/KR]; Gangbyeon Hyundai Apt., 101-708, Pungnap 2-dong, Songpa-gu, Seoul 138-042 (KR). **LEE, Young-Woo** [KR/KR]; Taesan 1st Apt. 103-1508, Gosaek-dong, Gwonseon-gu, Suwon-si, Gyonggi-do 441-728 (KR). **LEE, Yun-Gee** [KR/KR]; Daemyung Apt. 206-1007, Jangseong Maeul, Daehwa-dong, Ilsan-gu, Goyang-si, Gyeonggi-do 411-707 (KR).

(74) Agent: **CHO, In-Jae**; 3rd Fl., Janghyun Bldg., 637-23 Yeoksam-dong, Gangnam-gu, Seoul 135-909 (KR).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

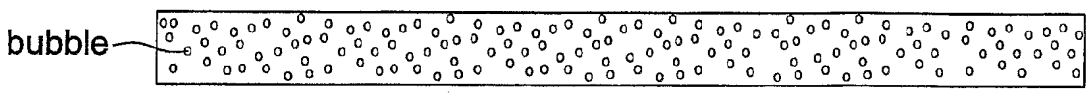
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/044285 A1

(54) Title: ANTI-ADHESION AGENT WITH GAS BUBBLE



(57) Abstract: The present invention relates to an anti-adhesion barrier with gas bubbles, more particularly, to porous materials for preventing adhesion of tissues, which are characterized in comprising bio-derived polymers and/or non bio-derived and biocompatible polymer and/or derivatives thereof as main components and having a structure with gas bubbles when swollen in water. As the porous materials for anti-adhesion according to the present invention, bio-derived or non bio-derived and biocompatible materials are used to minimize foreign material reactions; manufactured as the structure with gas bubble to promote physical barriers; staying for a given period in a human body to be degraded completely and absorbed, thereby not disturbing the healing of a post-operation wound; and giving the best convenience when applied to operation areas.

ANTI-ADHESION AGENT WITH GAS BUBBLE

Technical Field

The present invention relates to an anti-adhesion barrier with gas bubbles, more particularly, to porous materials for preventing adhesion of tissues, which are characterized in comprising bio-derived polymers and/or non bio-derived and biocompatible polymer and/or derivatives thereof as main components and being structured with bubbles when swollen in water.

Background Art

Adhesion may occur during the healing of tissue injuries occurred by inflammation, wound, chafing or surgery, wherein excessive tissue generation or extravasated bloods clotting promote sticking of the organs or tissues, which should be separated. In reality, such adhesion may occur after every operation and be a cause of serious clinical sequela.

These adhesions generally occur at the frequency of 67% to 93% after abdominal surgery. According to the U.S. survey information, as sequela occurred by post-operation adhesions, 49% to 74% of enterocleisis, 15% to 20% of infertility, 20% to 50% of chronic pelvic pain and 19% of

enterobrosia in a succeeding surgery have been known

These adhesions are initiated from a fibrin generated during the blood clotting process among exudates after a surgery. For several days afterwards, various cell factors are formed in the mother fibrin and are subsequently replaced by vascular granulation tissues including macrophages, fibroblasts and giant cells. After 4 days post-operation, most of fibrins disappear, and more fibroblasts and collagen are formed. During 5 to 10 days post-operation, the fibroblasts are incubated within adhesion, and then after 2 weeks, fibroblasts are mainly existed therein. After one or two months, the fibrillar collagens form a discontinuous bundle.

The peritoneal adhesion mechanism in abdominal surgery is specifically described in the thesis written by Granger (Granger DA, Incidence and causes of pelvic adhesion, Infert. Reprod. Med. Clin. North Am., 1994; 5(3):391-404). According to the Granger, a peritoneum is consisted of two layers of outside mesothelium and lower substrate(stroma). When the peritoneum is damaged, the lower substrate(stroma) is exposed, so that a vasoactive kinins and histamine are immediately released by the macrophage.

These materials increase locally the capillary permeability and form serosanguineous matrix including

inflammatory cells. These cells can produce cytokine and growth factors. Although their functions are not known clearly, a rat cecal abrasion model suggests that the interleukin-1 (IL-1) plays an initial media role in forming adhesions, when considering that the interlekin-1(IL-1) increases adhesion scores independently of dose or time. In addition, in an inflammatory effusion, the fibrin is abundant and blood clot is formed on the wound surface. As the fibrin is degraded (for three days), mesothelium is regenerated (for five days), and the wound is being healed. The degradation of fibrin, or fibrinolysis, is dependent upon the conversion of plasminogen to plasmin, which is a fibrin splitting enzyme, and this reaction is promoted by tissue plasminogen activator(tPA) existing in the mesothelium and the underlying stroma. However, if fibrinolysis does not occur, the inflammatory cells and the fibroblasts enter the fibrin matrix to promote adhesions.

Some of the generally adopted methods of reducing such adhesions include; minimizing the wound at operation, using an anti-inflammatory drug, promoting fibrin degradation and separating injured surfaces by barriers. In recent years, physical barriers for preventing the adhesions of fibrin and cell have been developed and used.

To be an effective barrier for preventing adhesions, during the healing of organs or tissues, it should act as

an effective physical barrier while not negatively influencing the healing of a wound and also prevent the forming of an adhesion between adjacent tissues. Also, after healing a wound for a given period, it should be degraded or absorbed to be removed and the material for a barrier itself or its degradation product should be innocuous to a human body.

The anti-adhesion barriers used for these barriers can be divided into two large classes in a view of their types: the first is a solution type barrier including a gel type and the second is a membrane type barrier including a film type, a non-woven type and a sponge type.

The solution type materials for preventing adhesions include lactated Ringer's solution, dextran-70 solution, heparin solution, sodium carboxymethyl cellulose solution ("CMC" is used hereinafter), sodium hyaluronate ("HA" is used hereinafter) solution, chondroitin sulphate solution, polyethylene glycol solution, ploxamer solution and the like.

The dextran-70 has high molecular weight and it is used as 32% solution of dextrose. The main mechanism lies in inducing the tissues to be floated away from each other. The CMC solution is water-soluble polymer which can form a viscous barrier between adjacent serous membrane surfaces.

The HA solution has ability to make the serous

surface coated and smoothened, and potentially to prevent post-operation adhesions. The animal study using a HA solution has proved that it reduced adhesion formation in abdominal cavity (Siholzman, MD. 1994). However, these biopolymer solutions are absorbed in vivo too fast, so the desired anti-adhesion effect is not achieved.

Meanwhile, since the polyethylene glycol and the like, which are synthetic polymers, are not degraded in vivo, only low molecular weight materials can be used to be absorbed and discharged through metabolic pathway. However, the disadvantage is that using only the materials of low molecular weight results in fast absorption, so that it cannot function as an effective barrier to prevent adhesions for an extended period of time.

The membrane type anti-adhesion barrier includes oxidized-regenerated cellulose ("ORC" hereinafter), expanded polytetrafluoroethylene ("ePTFE" hereinafter), and films consisted of HA and sodium carboxymethyl cellulose("CMC" hereinafter). The oxidized-regenerated cellulose has been originally introduced as a hemostatic agent and shown to reduce adhesion formation after cecal trauma(injury) of a rat but it was ineffective unless the bleeding was completely stopped.

In addition, Arora et al. reported that the oxidized-regenerated cellulose induced immune responses accompanying

macrophage, eosinophils, foreign body giant cell and the like(Arora et al. 1994; Haney & Doty 1992).

The ePTFE is in a sheet form, which is chemically inactive, and prevents entry of cells. It is specifically designed as pericardium alternatives at pericardium surgery (Minale et al. 1988; Revuelta et al. 1985). However, since the membrane is safe to the tissues but non-bioresorbable, another operation of removing said membrane is required. Also, another disadvantage is that it must be completely fixed to the wounded area.

US Patent Nos. 5,017,229; 5,527,893; and 5,760,200, disclose water-insoluble films consisting of a hyaluronic acid (HA) and carboxymethyl cellulose, which are kinds of polysaccharides, and a chemical cross-linking agent. However, these films have disadvantages in that an extensive cleansing process to remove a large quantity of cross-linking agent is required; they are broken easily due to the rigidity at dry state; they are exceedingly transformed at water contact, so that during an operation, special caution has to be taken to avoid working with wetted gloves. Therefore, it is considered that a successful anti-adhesion barrier has not yet been developed up to now.

Disclosure of Invention

The first object of the present invention is to provide an anti-adhesion barrier which: minimizes or prevents adhesions of post-operation; prevents adhesion formation after the first operation; prevents adhesion reformation after the second operation for removing adhesions; is biodegradable and/or bioresoluble; and has gas bubbles when swollen in water so as to be discharged completely from the human body.

Another object of the present invention is to provide an anti-adhesion barrier which does not influence the curing of a wound after an operation and controls a set time to promote degradation and absorption in vivo, to prevent an adhesion formation during the healing of the wound.

The above object and the others of the invention will be achieved with reference to the following description according to the present invention.

To achieve these objects the invention provides an anti-adhesion barrier characterized in comprising a bio-derived polymer and/or non bio-derived and bio-compatible polymer and/or derivatives thereof as main components, and including gas bubbles when swollen in water.

Said bio-derived polymer includes one or more selected from the group consisting of: chondroitin sulfate,

dermatan sulfate, keratan sulfate, heparan sulfate and hyaluronic acid which are a kind of glycosaminoglycan, and proteoglycan including the same; collagen and its degradation product called gelatin; elastin, laminin, fibronectin, vitronectin, tenacin, entactin; heparin, hirudin, fibrin; phospholipids; and keratin.

Said non bio-derived and bio-compatible polymer includes one or more selected from the group consisting of: polylactic acid(PLA), polyglycolic acid(PGA) and copolymer thereof(PLGA); poly-ε-caprolactone, poly-N-isopropylacrylamide(PNIPAM) and copolymers thereof; cellulose derivatives such as polypeptide, oxidized regeneration cellulose, carboxyethyl cellulose(CEC), carboxymethyl cellulose(CMC) and the like; chitosan, chitin and derivatives thereof; glucan, sodium alginate, PEG and poloxamer consisting of PEG-PPG-PEG block copolymer; polyanhydride; polyacetal; polyketal; poly-ortho-ester; Polyphosphazene and the like.

Said gas bubbles may include the bubbles innocuous to a human body, and one or more selected from the group consisting of nitrogen, oxygen, carbon dioxide, helium and argon.

Said anti-adhesion barrier may be produced further comprising 0.1 to 10 weight% of bio-derived polymer; 0.1 to 10 weight% of non bio-derived and biocompatible polymer;

and 0.01 to 0.5 weight% of cross-linking agent; and the residual quantity of water. Said cross-linking agent may be one or more selected from the group consisting of carbodiimides, glycidyl ethers, vinyl sulphones, epoxides, and aldehydes.

The pore size of said anti-adhesion barrier may be 1 to 1000㎛. The density of said anti-adhesion barrier may be 0.01 to 0.7 g/ml. The porosity of said anti-adhesion barrier may be 10% to 500%.

The swelling ratio (the weight of a sponge after hydration /the weight of a sponge before hydration) may be 10 to 300.

The weight reducing rate of said anti-adhesion barrier after enzyme degradation for 24 hours may be 1% to 60%.

Said anti-adhesion barrier has a structure including gas bubbles, more preferably triple layer structure having compact structure in the both surfaces thereof. Furthermore, the structure may consist of compact layer/bubble layer/compact layer so as to maintain gas bubbles easily.

The invention will be described in more detail as follows.

The anti-adhesion barrier according to the present invention is produced by using bio-derived material to

minimize a foreign material reaction; including gas bubbles structure so as to stay in a human body for a while and be completely degraded and absorbed; not disturbing the healing of a wound after an operation; and being conveniently applicable to the surgery area.

The anti-adhesion barrier according to the invention is produced by mixing or chemically linking bio-derived polymer and non bio-derived and biocompatible polymer in a proper ratio to have gas bubble structure. The sponge acts as a barrier to prevent adhesions for the healing of a wound, in the end it is degraded and absorbed to disappear completely in a human body.

Said bio-derived polymer may be one or more selected from the group consisting of: chondroitin sulfate, dermatan sulfate, keratan sulfate, heparan sulfate and hyaluronic acid, which are a kind of glycosaminoglycan, and proteoglycan including the same; collagen and its degradation product the so-called gelatin; elastin, laminin, fibronectin, vitronectin, thrombospontin, tenacin, entactin; heparin, hirudin, fibrin; phospholipids; and keratin.

Said non bio-derived and biocompatible polymer includes one or more selected from the group consisting of polylactic acid(PLA), polyglycolic acid(PGA) and copolymer thereof(PLGA); poly-ε-caprolactone, poly-N-

isopropylacrylamide(PNIPAM) and copolymers thereof; cellulose derivatives such as polypeptide, oxidized regeneration cellulose, carboxyethyl cellulose(CEC), carboxymethyl cellulose(CMC) and the like; chitosan, chitin and derivatives thereof; glucan, sodium alginate, PEG and poloxamer consisting of PEG-PPG-PEG block copolymer; polyanhydride, polyacetal, polyketal, poly-ortho-ester, Polyphosphazene and the like.

The sponge structure of the present invention, which includes gas bubbles, is as shown in Fig. 1.

The anti-adhesion sponge or film proposed as a conventional physical barrier has disadvantages in that when used it sticks to a wounded area so that blood, cells, fibrin and the like, which are flowed out from the wound, become soaked through the sponge or the film, and thus it can not function as perfect barriers to the other tissues. However, the gas bubbles included in the sponge of this invention are in the closed state so as to maintain the gas bubble layer when swollen in water. Therefore, the gas bubbles included in the sponge can function as a barrier consisting of gas.

Since blood, cells or fibrin extruded from a wound has little possibility to soak into the anti-adhesion sponge with gas bubbles, it can show more certain anti-adhesion effect as a barrier.

In addition, controlling the porosity of gas bubbles included in the sponge of this invention can bring down the sponge degradation rate by enzyme reactions inside a human body, so which can prevent the foreign material reaction in a human body due to the improper use of a cross-linking agent for chemical cross-linked bond and the side reaction of chemical bond used for controlling the degradation rate.

The sponge with gas bubbles according to this invention can be produced at manufacturing step to include various gases in the bubbles thereof. Said gases include one or more selected from the group consisting of nitrogen, oxygen, carbon dioxide, helium and argon.

When the anti-adhesion barrier was used in a human body after an operation, these bubbles are not replaced and filled by body fluid to be maintained at the state of including gas, so they act as gas barriers. A method of producing an anti-adhesion barrier with these bubbles including structure is one or more methods selected from freeze drying, salt elution, emulsification, good solvent/non solvent mixing and a foaming agent addition. As the structure of bubble, a closed type bubble is most ideal but it can form the structure in which more than two bubbles well controlled are connected to each other for not being filled and replaced by liquid or body fluid.

Furthermore, the anti-adhesion barrier of this

invention can be cross-linked chemically to control the degradation rate in a human body. Activating agents for chemical cross-linking are selected from radical initiators, cation initiators and anion initiators. Among these reaction initiators, carbodiimides, glycidyl ethers, vinyl sulphones, epoxides, aldehydes and the like are preferable. For examples, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimides(EDAC), 1,4-butanedioldiglycidyl ether, divinylsulphone and the like are included.

Also as cross-linking methods, one or more methods selected from stirring, heating, UV, ultrasound, plasma, gamma ray and the like are used.

The feature of the anti-adhesion barrier according to this invention is that the property thereof is depending on the porosity (%), the pore size, the density and the swelling ratio.

The density of the anti-adhesion barrier according to this invention is preferably 0.01g/ml~0.7g/ml. In case of less than 0.01g/ml of density, it has a problem that the porous structures are too abundant to form the closed bubble layers, so the opened structures do not act as barriers preventing adhesions due to the soaked exudates occurred after an operation. When it exceeds 0.7g/ml, it has also other problem that the sponge structures are too

dense to include the porous bubbles.

In addition, the pore size of the anti-adhesion barriers according to this invention is preferably 1㎛~1000㎛, and the porosity is preferably 10~500%. When the above porosity exceeds 500%, it has a problem that the sponge degradation rate with gas bubbles is delayed by the enzyme reactions in a human body, so the anti-adhesion barrier is not degraded and absorbed within a given period. If less than 10%, it has also other problem that since the degradation by the enzyme reaction in a human body is too fast the anti-adhesion barrier is absorbed without functioning as barriers to prevent adhesions for a given period.

The swelling ratio of the anti-adhesion barrier of this invention (the weight after hydration/the weight before hydration) is preferably 10~300. If less than 10, it has a problem that the bio-degradation does not occur because the sponge can not absorb water. When it exceeds 300, the problem is that the sponge is dissolved in water when swollen, thus it can not include bubbles in the structure thereof.

The anti-adhesion barriers of this invention consist of bubble including structures, preferably triple structures including the compact surfaces on the both side. That is, the structure consisting of compact layer/bubble

layer/compact layer may be easy to maintain gas bubbles.

The method of manufacturing the closed sponge structure with gas bubbles can be selected one from or mixed together with a sponge hot pressing method, a sponge surface coating method, a method of hot pressing after coating sponge surface, a method of transcribing the film made of the same materials to the both sides of the sponge structure and then hot-pressing the same, or a method of melting thinly the both sides of the sponge structure and then cross-linking.

Brief description of the drawing

Figure 1 shows the sponge structure with gas bubbles for preventing adhesion according to the present invention.

Figure 2 is a photograph showing the swollen state of the anti-adhesion sponge according to the present invention before enzyme degradation.

Figure 3 is a scannng electron micrograph showing the swollen state of the anti-adhesion sponge according to the present invention before enzyme degradation.

Figure 4 is a photograph showing the state of the anti-adhesion barrier according to the present invention after enzyme degradation.

Figure 5 is a micrograph showing the state of the anti-adhesion sponge according to the present invention

after enzyme degradation.

Figure 6 is a photograph showing the state of the anti-adhesion film without gas bubbles after enzyme degradation.

Figure 7 is a micrograph showing the state of the anti-adhesion film after enzyme degradation.

Figure 8 is a scanning electron micrograph showing the state of the anti-adhesion sponge according to the present invention before enzyme degradation.

Figure 9 is a scanning electron micrograph showing the state of the anti-adhesion sponge according to the present invention after enzyme degradation.

Figure 10 is a scanning electron micrograph showing the state of the anti-adhesion film before enzyme degradation.

Figure 11 is a scanning electron micrograph showing the state of the anti-adhesion film after enzyme degradation.

Figure 12 is a graph showing the adhesion grade according to the animal experiment of the sponge of the present invention, comparing with a film.

Figure 13 is a graph showing the adhesion strength according to the animal experiment of the sponge of the present invention, comparing with that of a film.

Figure 14 is a graph showing the adhesion area

according to the animal experiment of the sponge of the present invention, comparing with that of a film.

Modes for Carrying Out the Invention

The invention is described in more detail in the following examples but these examples are given by was of illustration and are not intended to limit the invention in any way.

[Example 1]

Manufacturing of a sponge for anti-adhesion by a hot pressing method

A solution of hyaluronic acid of 1% and a solution of CMC of 1% were mixed in the ratio of 1:1. Afterwards, freeze drying, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(EDAC) of 0.25% w/w (to sponge weight) was added to a mixture solution of acetone and water(9:1), and then cross-linked for 12 hours or more. After that, it was washed sufficiently with ethanol over 3 times and then dried. The dried sponge was heated at 120℃ and pressed to 2mm in thickness. The sponge made as above is not dissolved but swollen in water as shown in Figs. 2 and 3, and when swollen, numerous bubbles are produced.

[Example 2]

Manufacturing of a sponge for anti-adhesion by a surface coating method

The sponge manufacturing method till the process of freeze drying is the same as example 1. A mixture solution of hyaluronic acid and carboxymethyl cellulose was coated on the sponge surface. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide(EDAC) of 0.25 % w/w was added to the mixture solution of acetone and water(9:1), and then cross-linked for 12 hours or more. After that, it was washed sufficiently with ethanol over 3 times and then dried.

[Example 3]

Manufacturing of a sponge for anti-adhesion by pressing method succeeding a surface coating

The same method with example 2 to the process of washing with ethanol over 3 times and then drying was taken. The dried sponge was heated at 120℃ and pressed to 2mm in thickness.

[Example 4]

Hot-pressing after manufacturing a sponge for anti-adhesion by a salt elution method

A solution of hyaluronic acid of 1% and a solution of CMC of 1% were mixed in the ratio of 1:1. Afterward, freeze drying, the mixture was immersed in a mixture

solution of ethanol and distilled water (9:1). After that, using 1N HCl the pH thereof was controlled to 2.5. After acid treatment for 6 hours, the mixture was washed with solutions of ethanol and distilled water in ratio of 5:5, 4:6, 3:7 and 2:8 respectively. Until the pH thereof went to 6.8~7.2 it was washed several times and finally with ethanol. After washing, the dried sponge was heated at 120℃ and pressed to 2mm in thickness.

[Example 5]

Manufacturing a sponge for anti-adhesion by a hot-pressing method

A solution of chontroitin sulfate of 1% and a solution of CMC of 1% were mixed in the ratio of 1:1. The next method to heat the dried sponge at 120℃ and press it to 2mm in thickness was the same with that of example 1.

[Example 6]

Manufacturing a sponge for anti-adhesion by a hot-pressing method

A solution of collagen of 1% and a solution of CMC of 1% were mixed in the ratio of 1:1. The next method to heat the dried sponge at 120℃ and press it to 2mm in thickness was the same with that of example 1.

[Example7]

Manufacturing a sponge for anti-adhesion by a hot-pressing method

A solution of gelatin of 1% and a solution of CMC of 1% were mixed in the ratio of 1:1. The next method to heat the dried sponge at 120℃ and press it to 2mm in thickness was the same with that of example 1.

[Example 8]

Hot-pressing after manufacturing a sponge for anti-adhesion by a salt elution method

Chitosan was dissolved in a solution of acetic acid of 4% to make a solution of 1%. A solution of chitosan of 1% and a solution of CMC of 1% were mixed in the ratio of 1:1 Afterwards, freeze drying, the mixture was immersed in a mixture solution of ethanol and distilled water in the ratio of 9:1. Salts were eluted from the mixture for over 24 hours. It was washed with solutions of ethanol and distilled water in the ratio of 5:5, 4:6, 3:7 and 2:8 respectively. After washing several times to 6.8 ~ 7.2 of pH, the sponge was washed finally with ethanol. The dried sponge was heated at 120℃ and pressed to 2mm in thickness.

[Example 9]

Hot-pressing after manufacturing a sponge for anti-adhesion

by an ion-binding method

A solution of sodium alginate of 1% and a solution of CMC of 1% were mixed in the ratio of 1:1. Afterward, freeze drying, the mixture was immersed in the coagulation of calcium chloride of 20% dissolved in ethanol. After the ion reaction for two hours, it was washed completely with ethanol and then the dried sponge was heated at 120℃ and pressed to 2mm in thickness.

[Example 10]

Surface coating after manufacturing a sponge for anti-adhesion by a salt elution method

In three neck flask, lactic acid(3.78g), glycolic acid(1.22g), polyethylene glycol 2000(2g), stannous octate(0.03g) and toluene(80ml) were inserted and reacted under nitrogen at 110℃ for 60 hours. Afterward, it was immersed in diethyl ether, and then dissolved in a solution of chloroform more than 3 times. After a vacuum drying of final product, sodium chloride of 88 weight% thereto was mixed. The mixture was dissolved in chloroform and poured into a mold till 2mm in thickness. The chloroform was removed in an oven of 40~60℃. By washing water several times the sodium chloride was removed to result in the form of porous sponge. To make the both sides of the sponge compact, the chloroform was coated on the surface and then

removed in an oven of 40~60℃.

[Comparative example]

Manufacturing a film without gas bubbles for anti-adhesion

A solution of hyaluronic acid of 1% and a solution of CMC of 1% were mixed in the ratio of 1:1. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide(EDAC) of 0.25% to weight of solid material of the mixture solution was added to the mixture. Afterward, it was cross-linked for over 12 hours and dried.

[Experimental example 1]

Comparison of the properties of the films without gas bubbles and the sponge with gas bubbles

The properties of the sponges with gas bubbles of said examples 1~10 and the film without gas bubbles of comparative example were compared therewith and the results are shown in the following table 1. The results show the similar properties as the following table 1 when the sponges with gas bubbles according to the examples 1~10 and the film without gas bubbles of comparative example were compared.

Table 1

	Sponges							Film			
	E.1	E.2	E.3	E.4	E.5	E.6	E.7	E.8	E.9	E.10	C.E.
D. (g/ml)	0.13	0.15	0.17	0.08	0.05	0.19	0.21	0.17	0.11	0.24	0.34
S.D (Ws/Wd)	198.87	169.58	154.46	135.40	121.44	184.36	175.23	154.32	194.39	121.22	177.73
P. (%)	159.26	123.27	107.17	130.12	144.41	121.74	99.65	100.88	137.46	155.37	

D is density; S.D. is swelling ratio; P. is porosity.

[Experimental example 2]

Enzyme degradation comparison of the sponges with gas bubbles and the film without gas bubbles.

After manufacturing an enzyme solution (hyaluronidase) of 10 unit per hyaluronic acid of 1mg, the sponges with gas bubbles of the examples 1~4 and the film without gas bubbles of the comparative example were immersed in the enzyme solution. Afterward, it was carried out by the enzyme reaction in a carbon dioxide incubator of 37℃ for 24 hours. The properties when before and after degradation in vitro were compared. The results are shown in the following tables 2 and 3.

The properties before/after enzyme degradation of the sponges with gas bubbles according to the examples 1~4 and the film without gas bubbles of comparative example were compared respectively. The results as the table 2 show that the difference between examples and comparative example is not big. However, the properties after enzyme degradation,

in a view of weight changing, show the weight loss of the comparative example more than that of the examples. Thus, from that, it can be taken that the film without gas bubble layers is rapidly degraded by enzyme reaction.

Table 2

The properties before enzyme degradation

	Sponge				Film
	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Com.Ex.
Density(g/ml)	0.13	0.15	0.17	0.08	0.34
Swelling ratio(Ws/Wd)	198.87	169.58	154.46	135.40	177.73
Porosity(%)	159.26	123.27	107.17	130.12	

Table 3

The properties after enzyme degradation

	Sponge			Film	
	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Com.Ex.
Weight reducing rate(%)	35.63	23.63	40.41	41.93	54.40
Density(g/ml)	0.14	0.21	0.20	0.22	0.24
Swelling ratio(Ws/Wd)	171.95	177.71	146.64	165.08	121.02
Porosity(%)	135.10	56.00	62.33	84.32	

[Experimental example 3]

Measuring adhesion grade, adhesion strength and adhesion area of the sponges with gas bubbles and the film without gas bubbles

The adhesion was forced to occur in the cecum and the peritoneum of a rat. The effect of preventing adhesions by the anti-adhesion sponges with gas bubble layers of the example 1 and the film without gas bubbles of the comparative example was observed. The adhesion grade and

the adhesion strength were evaluated according to the following standard and the adhesion area was calculated by measuring the length of width and height.

The experiment results are shown in Figs. 12 ~14.

<Adhesion grade>

0: No adhesion

1: When focal adhesion occurs in a little

2: When focal adhesion occurs in a large

3: When sheet adhesion occurs

4: When sheet adhesion occurs deeply

5: When sheet adhesion occurs together with blood vessel.

<Adhesion strength>

0: When adhesion does not occur

1: When adhesion is in a form of film and can be separated by very little power.

2: When adhesion requests for middle power

3: When adhesion can be separated by sufficient power.

4: When adhesion is too strong to be separated or requests for very big pressure.

As known from the following Figs. 12~14, for the sponge with gas bubbles of example 1 according to this invention and the film without gas bubbles of comparative

example, the adhesion grade, the adhesion strength and the adhesion area are lower than for the control which was not treated at all. Also, the sponge with gas bubbles of example 1 showed the adhesion grade and the adhesion strength relatively lower than that of the film of comparative example. That is, it is shown that the sponges with gas bubbles are more effective to prevent adhesions.

Industrial Applicability

As described above, the anti-adhesion barrier of this present invention is useful invention wherein this invention uses bio-derived materials to minimize foreign reactions; produces gas bubble structures to stay for a given period in a human body, and then to be degraded and absorbed for not disturbing the healing of a post-operation wound; and thus gives the best convenience when applied to operation areas.

What is claimed is:

1. An anti-adhesion barrier comprising bio-derived polymer and/or non bio-derived and biocompatible polymer and/or derivatives thereof as main components, of which structure has bubbles when swollen in water.

2. The anti-adhesion barrier of claim 1, wherein 0.1 to 10 wt% of bio-derived polymer; 0.1 to 10 wt% of non bio-derived and biocompatible polymer; 0.01 to 0.5 wt% of reaction initiator are more included; and water in the residual quantity.

3. The anti-adhesion barrier of claim 1, wherein bio-derieved polymer includes one or more selected from the group consisting of chondroitin sulfate, dermatan sulfate, keratan sulfate, heparan sulfate and hyaluronic acid, and proteoglycan including the same; collagen and its degradation product the so-called gelatin; elastin, laminin, fibronectin, vitronectin, thrombospontin, tenacin, entactin; heparin, hirudin, fibrin; phospholipids; and keratin

4. The anti-adhesion barrier of claim 1, wherein the non bio-derived and biocompatible polymer includes one or more selected from the group consisting of polylactic

acid(PLA), polyglycol acid and copolymers thereof; poly-ε-caprolactone, poly-N-isopropylacrylamide and copolymers therof; cellulose derivatives such as polypeptide, oxidized regenerated cellulose, carboxyethyl cellulose(CEC) and carboxymethyl cellulose(CMC); chitosan, chitin and derivatives thereof; glucan, sodium alginate; PEG, poloxamer consisting of PEG-PPG-PEG block copolymer; and polyanhydride, polyacetal, polyketal, poly-ortho-ester, polylphospazen.

5. The anti-adhesion barrier of claim 2, wherein the reaction initiator includes one or more selected from the group consisting of carbodiimdes, glycidyl ethers, vinyl sulphones, epoxides and aldehydes.

6. The anti-adhesion barrier of claim 1, wherein the bubbles are gathered with bubbles innocuous to a human body.

7. The anti-adhesion barrier of claim 1, wherein the bubbles include one or more selected from the group consisting of nitrogen, oxygen, carbon dioxide, helium and argon.

8. The anti-adhesion barrier of claim 1, wherein the pore size is 1㎛ to 1000㎛.

9. The anti-adhesion barrier of claim 1, wherein the density of said anti-adhesion barrier is 0.01 to 0.7g/ml.

10. The anti-adhesion barrier of claim 1, wherein the porosity of said anti-adhesion barrier is 10% to 500%.

11. The anti-adhesion barrier of claim 1, wherein the swelling ratio of said anti-adhesion barrier is 10 to 300.

12. The anti-adhesion barrier of claim 1, wherein the weight reducing rate after enzyme degradation of said anti-adhesion barrier for 24 hours is 1 to 60%.

13. The anti-adhesion barrier of claim 1, wherein said anti-adhesion barrier has bubble including structures, which is provided by heating and pressing.

14. The anti-adhesion barrier of claim 1, wherein said anti-adhesion barrier has bubble including structures, which is provided by coating the surface thereof.

15. The anti-adhesion barrier of claim 1, wherein the anti-adhesion barrier has bubble including structures, which is provided by transcribing the films made of the

same material on the both sides of the sponge structure, heating and pressing.

16. The anti-adhesion barrier of claim 1, wherein the anti-adhesion barrier has bubble including structures, which is provided by melting the both sides of the sponge thinly and cross-linking.

17. The anti-adhesion barrier of any claim among the claim 1 to 16, wherein the anti-adhesion is in the form of a sponge.

FIG. 1

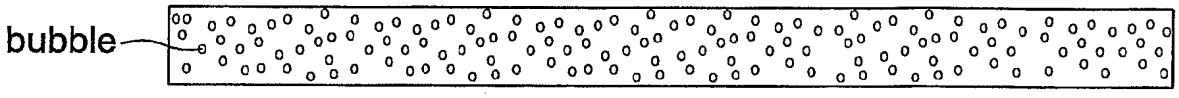


FIG. 2

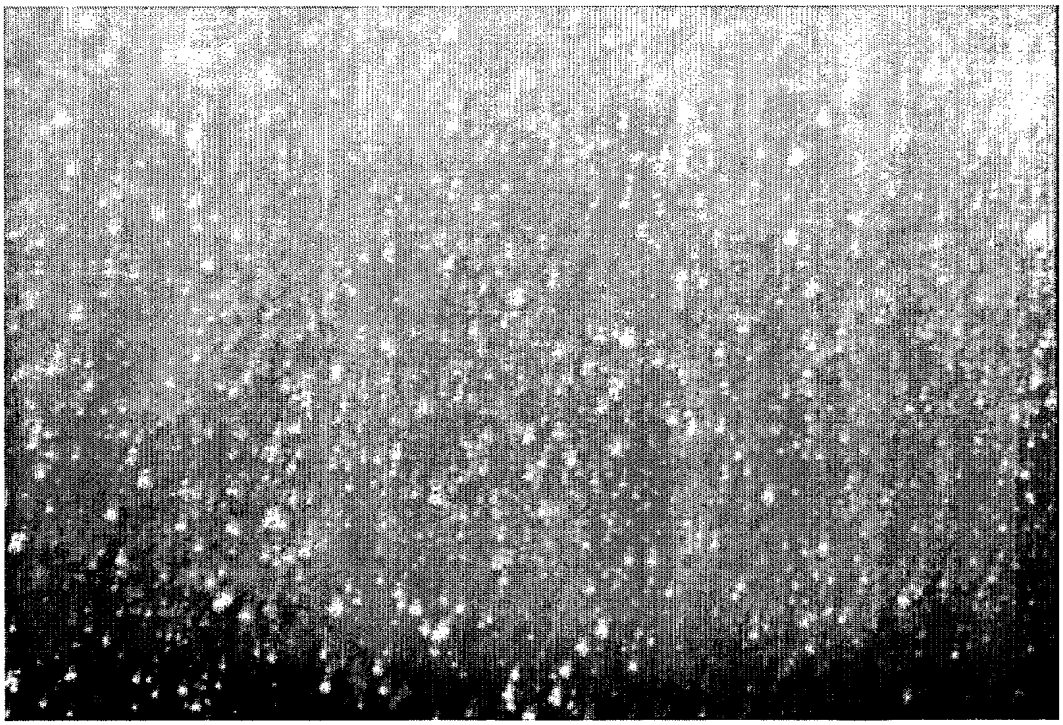


FIG. 3

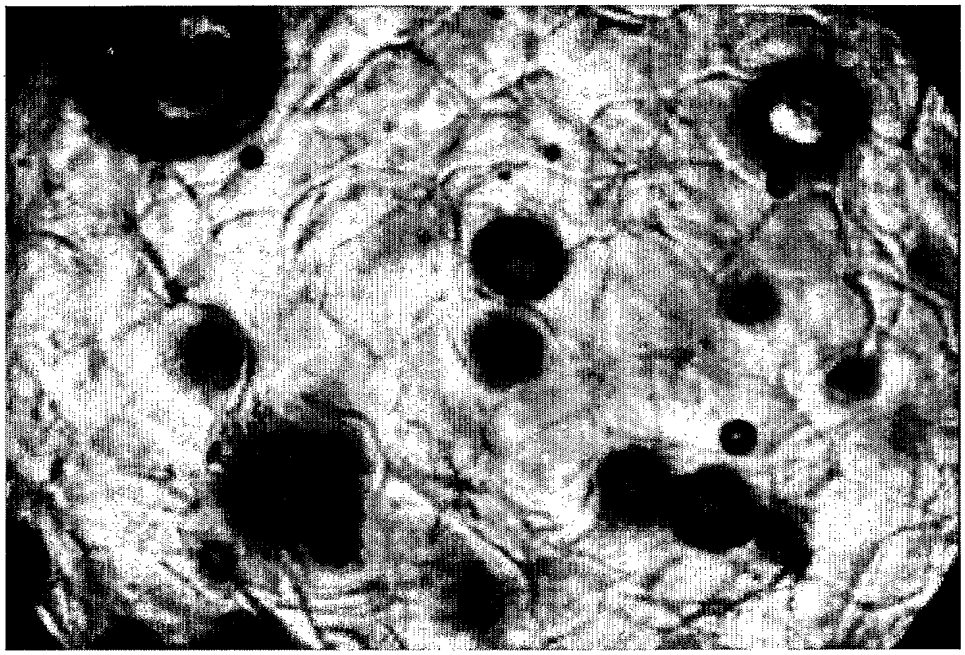


FIG. 4

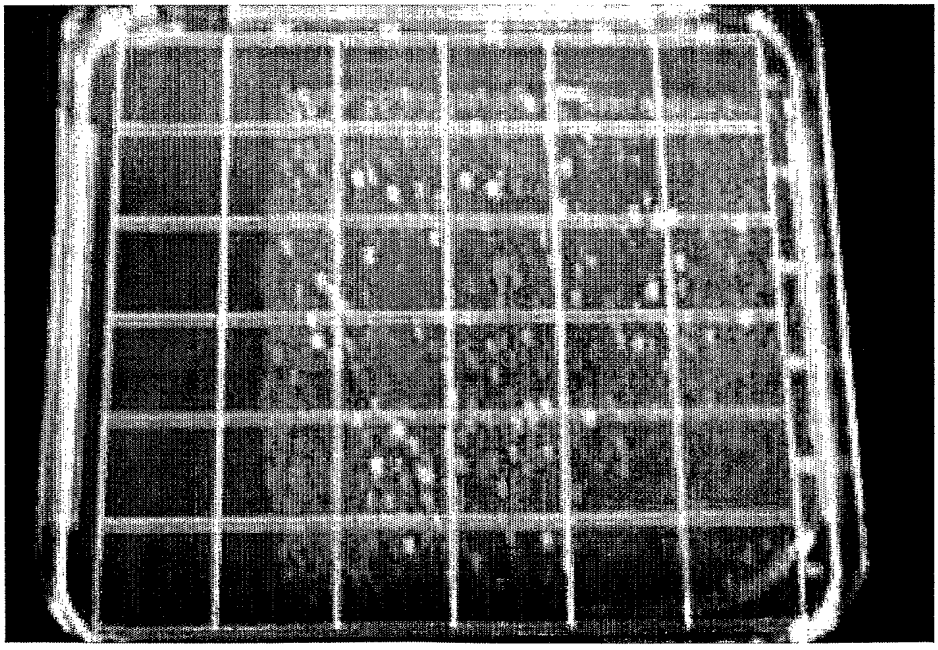


FIG. 5

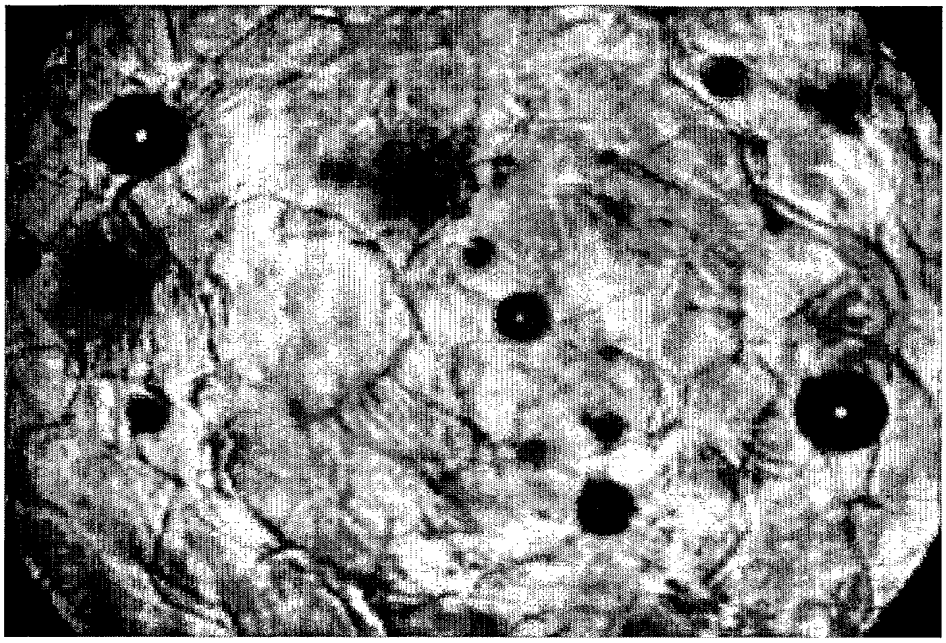


FIG. 6

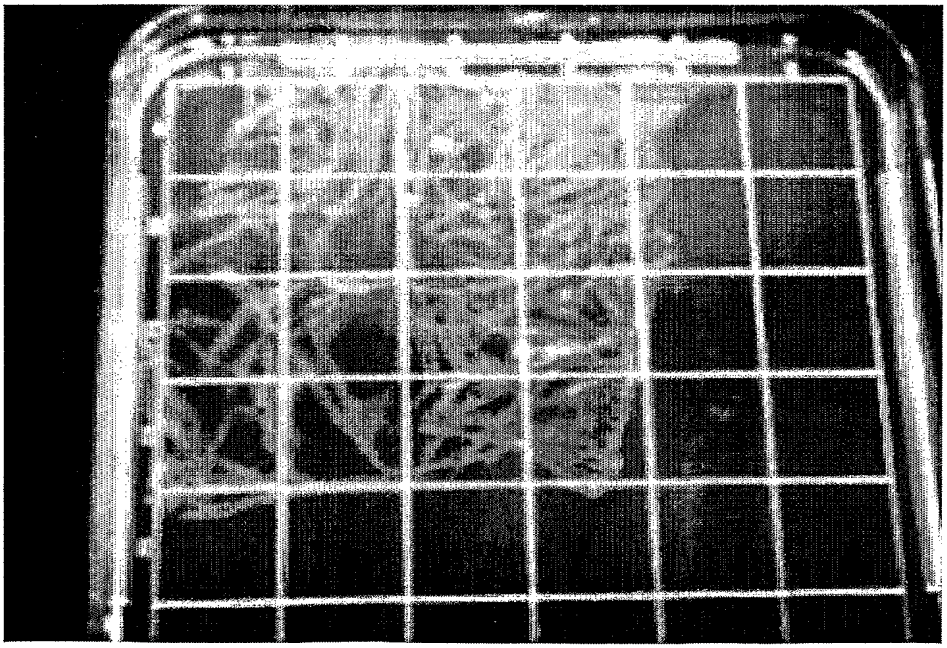


FIG. 7

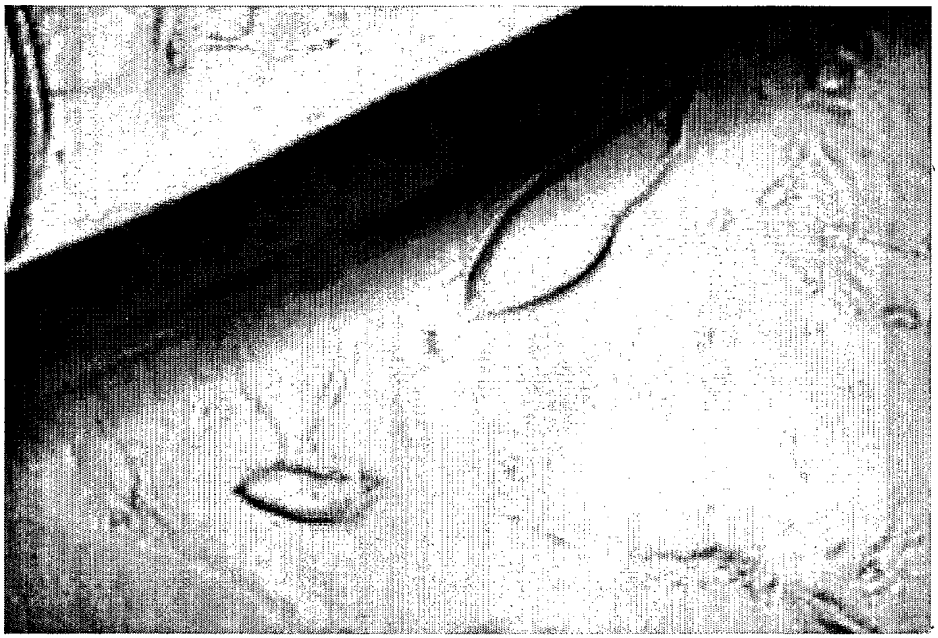


FIG. 8

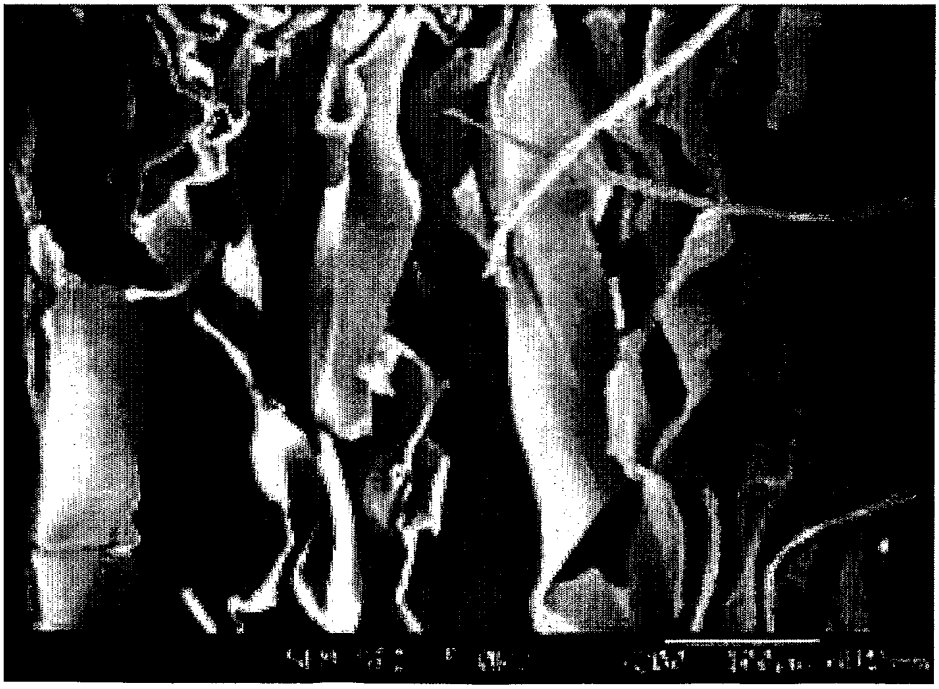


FIG. 9

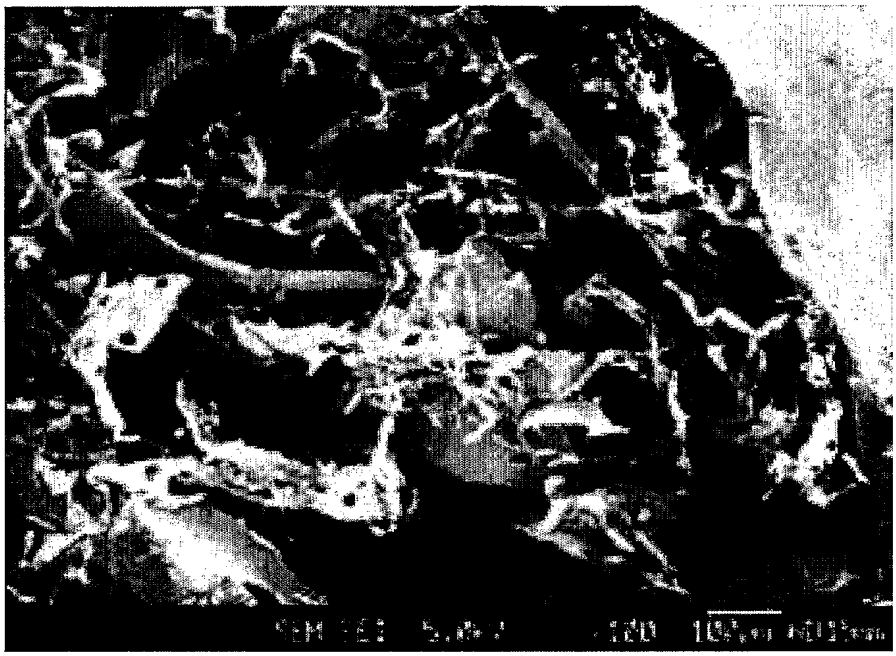


FIG. 10

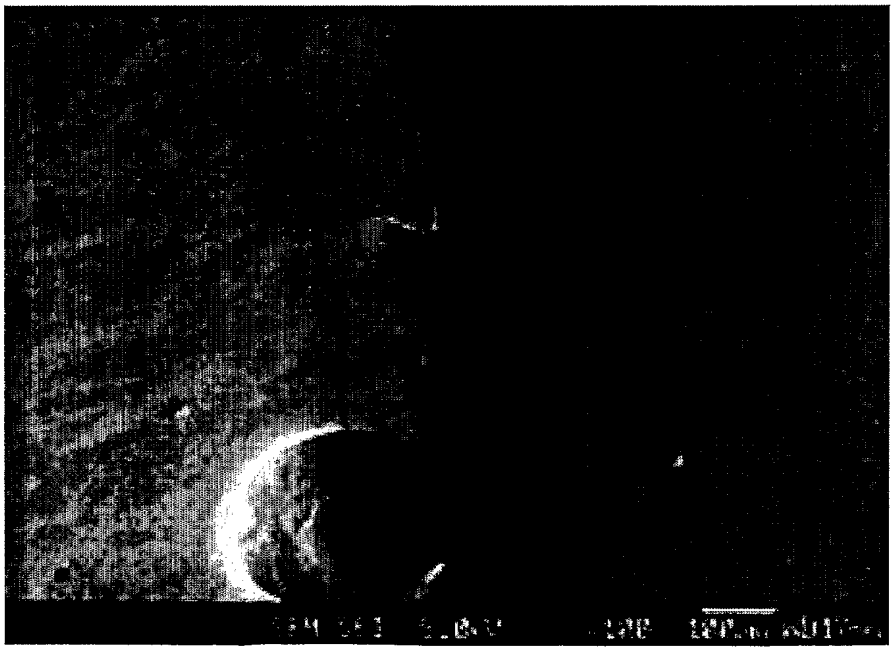


FIG. 11

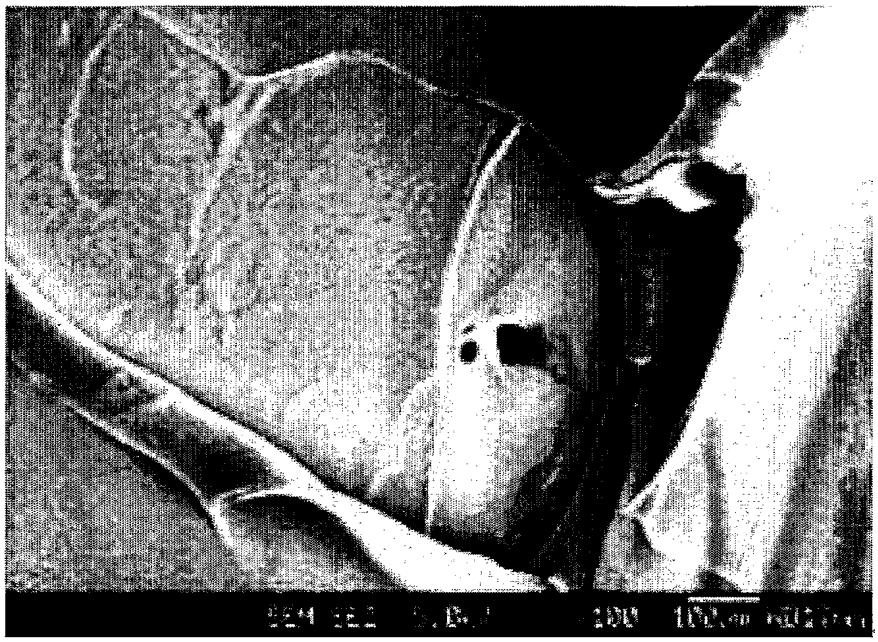


FIG. 12

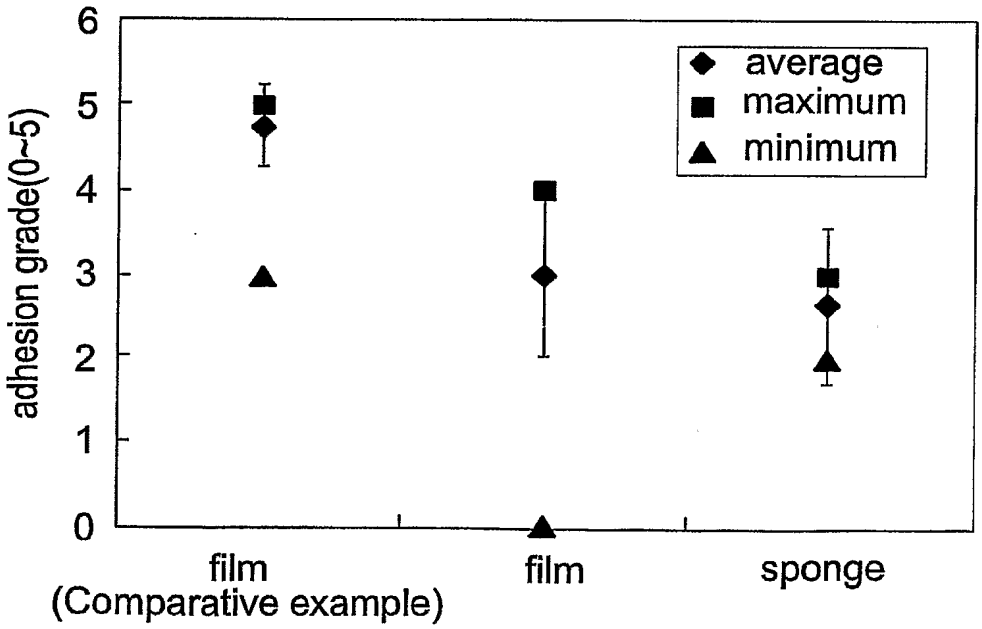

6
5
4
3
2
1
0
adhesion grade(0~5)
average
maximum
minimum
film
(Comparative example)
film
sponge

FIG. 13

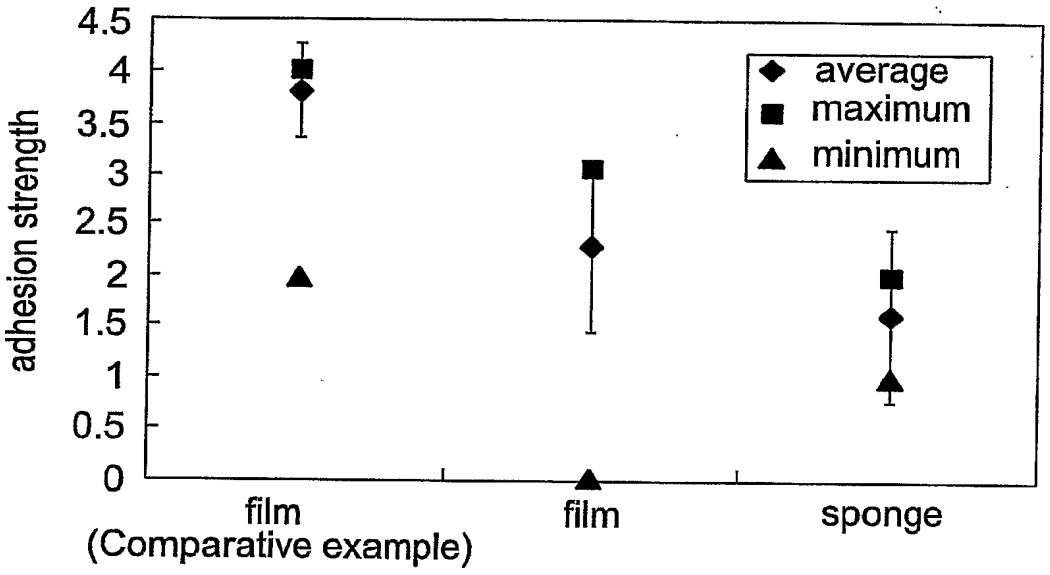
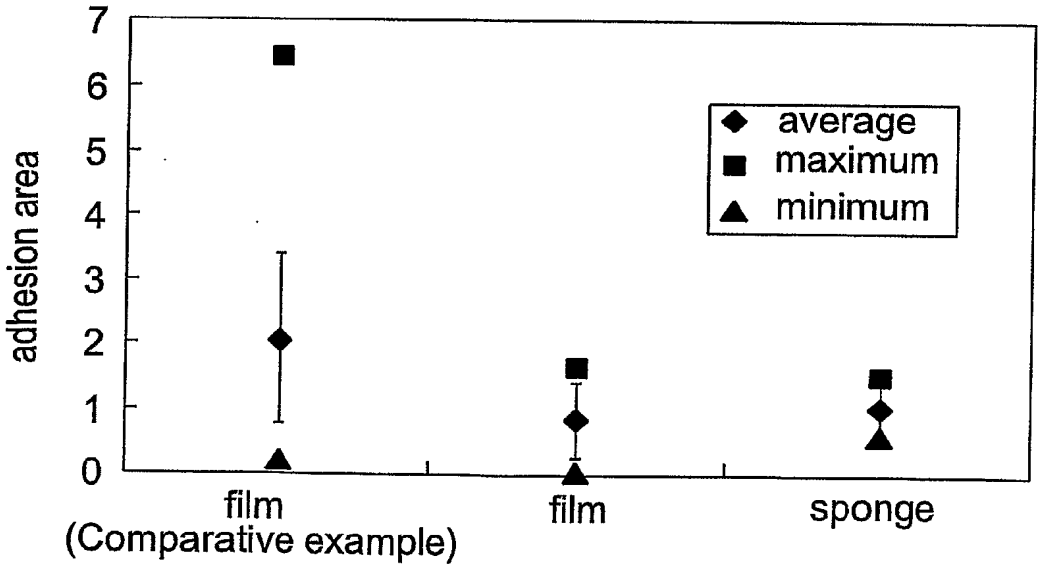

4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
adhesion strength
average
maximum
minimum
film
(Comparative example)
film
sponge

FIG. 14


7
6
5
4
3
2
1
0
adhesion area
average
maximum
minimum
film
(Comparative example)
film
sponge

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/002837

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 31/74

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 : A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
KOREAN PATENTS AND APPLICATIONS FOR INVENTIONS SINCE 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)
PubMed, WPI, USPTAFULL, JAPIO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KR 99-64638 A (AMITIE CO., LTD.) 05 August 1999. See entire document.	1-17
X	WO 00-49084 A1 (DENKI KAGAKU KOGYO KABUSHIKI KAISA) 24 August 2000. See entire document.	1-17
Y	KR 02-31351 A (SAMYANG CORPOTATION) 01 May 2002. See entire document.	1-17
Y	KR 02-11955 A (AMITIE CO., LTD.) 09 February 2002. See entire document.	1-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 FEBRUARY 2005 (15.02.2005)	**17 FEBRUARY 2005 (17.02.2005)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701,
Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
Yoon, Kyung Ae
Telephone No. 82-42-481-5605

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/002837

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 00-49084 A	24.08.00	US6638538B1	28.10.03
		CA2371833AA	24.08.00
		EP117446A1	23.01.02
		AU773826B2	10.06.04